IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Modulating The Gut Microbiome - Brain Axis: Therapeutic Potential of Probiotics For Brain Health

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ABSTRACT:

The complex communication network that exists between the gastrointestinal tract and the central nervous system, known as the gut microbiome-brain axis, has a major impact on behaviour and brain function. Beneficial living microorganisms known as probiotics have shown promise in modulating this axis and providing possible therapeutic advantages for mental health. This review explores our present understanding of the processes by which probiotics affect the gut-brain axis, with particular attention to immunological regulation, neurotransmitter synthesis, and gut barrier integrity enhancement. According to clinical research, some probiotic strains can lessen the signs and symptoms of mental illnesses like stress, anxiety, and depression. This study objectively assesses the data pertaining to probiotics effectiveness in various situations, stressing both their possible advantages and disadvantages, including strain-specific side effects, the need for proper dosage, and long-term safety. By synthesizing insights from microbiology, neuroscience, and clinical research, this review aims to provide a comprehensive overview of probiotics as an innovative, adjunctive strategy for improving brain health. It seeks to pave the way for future investigations and the development of targeted probiotic therapies in the field of neuropsychiatry.

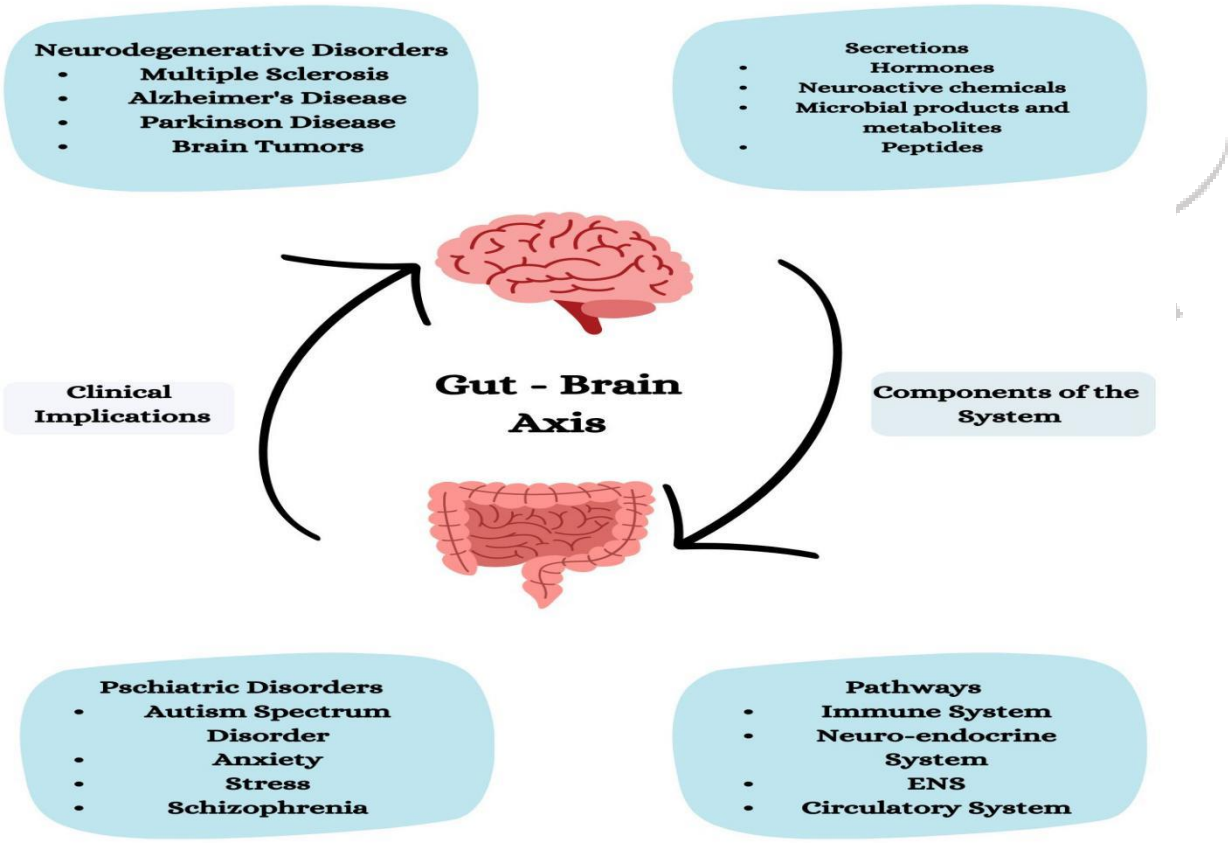
Key Words: Gut- Microbiome, Probiotics, Brain - Axis, Neuro - immune pathways, Neural- communication pathways.

INTRODUCTION:

Trillions of bacteria reside in the human gut and are essential to the physiology and health of the host. Dysbiosis, or disruptions in the balance of microbial composition, has been associated with an array of illnesses [1]. The gut-microbiota-brain axis's essential features include its bidirectionality, which allows signals to flow from the brain to the gut and vice versa [2]. The gut microbiota's contribution to neurodegenerative illnesses is becoming more widely recognized [3]. Probiotics are described as live bacteria that, when taken in sufficient quantities, improve host health, according to the World Health Organization (WHO) [4]. The use of probiotics leads to the preservation of the gut barrier, the restoration of GM, modifications in metabolites originating from the microbiota, a decrease in inflammation, and the function of the hypothalamus pituitary adrenal (HPA) axis [5]. The intriguing prospect of working on and influencing the microbiota-gut-brain axis in order to treat a variety of difficult central nervous system disorders [6]. The aim of this article is to provide a brief summary of the beneficial effects of probiotics for mental health.

GUT- BRAIN AXIS:

The "gut-microbiota-brain axis" is a network of interactions influencing several biological systems that allows gut bacteria and the brain to communicate in both directions. It is crucial for maintaining the immune system's, endocrine system's, central, autonomic, and gastrointestinal system and enteric nerve systems [7]. The sympathetic and parasympathetic branches of the autonomic nervous system, the enteric nervous system (ENS), the neuroendocrine and neuroimmune pathways, and the central nervous system are all associated with communication with the gut microbes [8]. These biological networks contain neural pathways, the immune system, and chemical transmitters as direct and indirect means of communication [9]. The hypothalamic-pituitary-adrenal axis and the autonomic nerve system, specifically norepinephrine, are two ways in which the brain regulates gut function [10]. On the other hand, the gut regulates central nervous system (CNS) functioning by means of a range of metabolites and products formed from the microbiota, neuroactive agents, and gut hormones that pass via the vagus nerve, circulatory system, immune system, or enteric nervous system before arriving at the brain. The microbiome-gut-brain axis (MGBA) is the term for these pathways [11]. Local neurotransmitters like histamine and physiologically active catecholamines are produced by modulating afferent sensory neurons. The gut-brain axis may be impacted by the gut microbiota's influence on nutrition availability, which could change the way peptides are released from enteroendocrine cells. Dysbiosis of the gut microbiota can cause inflammation and the release of cytokines that can affect the gut-brain axis. Bacterial metabolites can pass the blood-brain barrier, impact the humoral system, and control microglia to promote cognitive development [12].



GUT – BRAIN AXIS

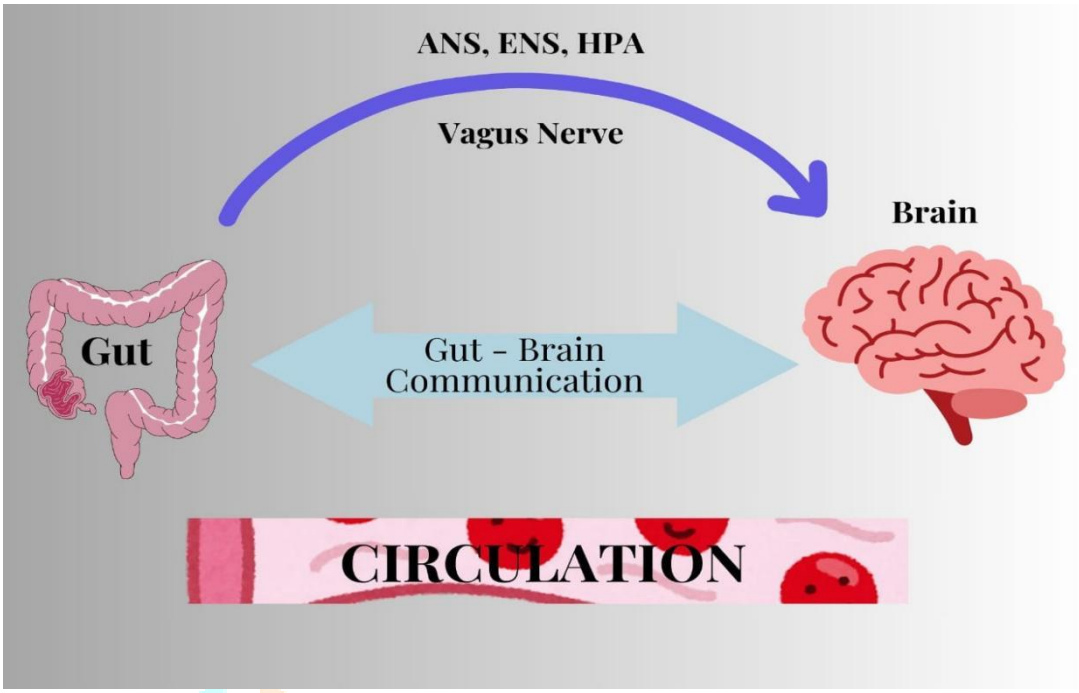
MICOBIAL-DERIVED METABOLITES AND PRODUCTS:

Through both "direct" and "indirect" chemical signaling with the neurological system, the gut bacteria can assist in modulating homeostasis [13]. Direct signaling: endogenous tryptophan and short-chain fatty acids (SCFAs) are two of the best-characterized metabolites [14]. Short-chain fatty acids bind to receptors that are connected to G proteins [15]. The primary components of short-chain fatty acids (SCFAs), which are lipids

made by gut microbes through the fermentation of carbohydrates, are butyrate, propionate, and acetate. By controlling immunological function, epigenetic and gene expression, and neuroplasticity, SCFA can have an impact on the central nervous system [16]. By maintaining brain integrity, SCFA affects learning and memory acquisition and supports mucosal serotonin release, glucose balance, lymphocyte function, and learning [14]. It is unknown if SCFAs from the gut can penetrate the blood-brain barrier (BBB) and affect brain function directly [17]. Mechanistically, research has documented connections between SCFAs and G-protein-coupled receptors (GPR) for a range of diverse roles, including GPR41 in enteric neurons and GPR43 in adipose tissues [18]. It has been proposed that acetate, a crucial SCFA generated by gut bacteria, controls appetite and crosses the blood-brain barrier to accumulate in the hypothalamus [17]. Butyrate reduces depressive-like behaviour and promotes repetitive behaviour, while propionate hinders social behaviour and alters histone acetylation and brain-derived neurotrophic factor (BDNF) expression [9, 19]. The conversion of dietary tryptophan to indole compounds through microbial metabolism also reveals that bacteria, especially some species of the Lactobacillus genus, are important for activating the aryl hydrocarbon receptor, which in turn regulates the cell cycle and promotes T-cell development [20]. It is crucial for encephalitogenic T cell responses, which trigger CNS autoimmunity [21].

NEURAL COMMUNICATION PATHWAY:

The brain and the intestines are physically connected by neural connections. The vagus nerve, which originates in the brainstem and innervates the gut and enteric nervous system, is the most prominent neural pathway among them [22]. The tenth cranial nerve, the vagus nerve, controls GI secretion, peristalsis, and satiation by extending from the brain into the gut's muscular and mucosal layers. The principal afferent pathway that communicates information about immunity, microorganisms and nutrients from the gut to the central nervous system is the vagus nerve, which consists primarily of sensory fibres. In contrast, the activation of vagal efferent fibers by the central nervous system (CNS) decreases the release of pro-inflammatory cytokines and initiates a systemic anti-inflammatory response. These multiple functions point to crucial brain-gut microbiota contact in both directions [23]. Via neuroimmune and neuroendocrine pathways, the microbiota may activate vagus nerve afferent sensory neurons to transmit messages to the brain [24]. The vagus nerve, as well as the central spinal and sacral afferent terminals, provide input to the gut [25]. The gastrointestinal tract's muscle and mucosa layers are innervated by vagus nerve fibers, which also detect and send sensory signals to the central nervous system [26]. Signals from the peripheral ends of the vagus nerve are transmitted to the central nervous system (CNS) by means of either mechanoreceptors that detect luminal volume or chemoreceptors that are activated by chemical stimuli, including hormones, neurotransmitters, and metabolites generated by endothelial cells (EECs) [27]. It is evident that the gut microbiota makes use of both vagus-dependent and vagus-independent signaling pathways. The intriguing function of the vagus nerve as a pathway for neurological pathogenesis and gut microbiota-brain connection [2].



GUT – BRAIN COMMUNICATION

IMMUNE SIGNALLING:

The gut microbiota has a major role in regulating the growth and function of the peripheral immune system. The gut microbiota and central nervous system possess an impact on the immune system both directly and indirectly [1]. Through the systemic immune system, the gut microbiota and the brain also communicate through circulating cytokines, including interleukin 6 and tumour necrosis factor-a (TNF-a) [29]. Either brain-resident immune cells can create cytokines and chemokines, or they can penetrate the blood-brain barrier directly to enter the central nervous system [30]. Numerous neuropsychiatric disorders, such as depression, anxiety, and ASD, are associated with elevated peripheral inflammation and altered immunological signaling in the brain due to changes in systemic immunity [31]. The gut microbiome demonstrates the possible influence of relationships between outcomes in the brain and systemic immunity [32].

MECHANISM OF ACTION OF PROBIOTICS IN BRAIN:

B cells produce IgA, which is a potential way that probiotics may enhance the gut immune function. Probiotics such as Lactobacillus casei, acidophilus, rhamnosus, plantarum and lactis, and Streptococcus thermophilus have been demonstrated to increase the number of intestinal IgA-producing cells in a dose-dependent manner. Probiotics can stimulate clonal growth of B cells driven to release IgAs while not impacting the CD4+ T cell population [33]. Probiotics use a combination of specialized adhesion molecules found in their bacterial wall components and non-specific physical binding, like hydrophobic contacts. Mucus-binding proteins (Mub) and mucin-binding proteins (MucBP) are surface-adhesive proteins with mucin-binding domains. Fimbriae or pili, including Type IV pili and/or minor fiber components known as Sortase-mediated pilus assembly (Spa)-A,-Band-C, are thin proteinaceous extensions from bacterial cells and fibronectin is also present. Probiotics can aid in the colonization of commensal microbes [34]. As a result, modifying the activity and/or composition of the intestinal immune cells and microbial population can provide the beneficial effect of probiotics on immunological activities [35]. The molecular mechanisms and components that mediate probiotic-immune cell interactions have been partially discovered. Probiotic proteins and molecules on the cell's surface and envelope have been found to play key roles in action [36]. Probiotics may increase the expression of TLR-2 and mannose CD206 receptors on DCs and macrophages, stimulating the adaptive immune response [37]. Several studies have identified bacterial proteins and non-proteinaceous compounds, such as teichoic acids (TA), lipoteichoic acids (LTA), exopolysaccharides (EPS), and peptidoglycan (PG), as molecular effectors that play a role in immune modulatory pathways [38].

Probiotics function as well as antimicrobial agents by creating short chain fatty acids (SCFA), organic acids, hydrogen peroxide, and bacteriocins, which reduce pathogenic microorganisms in the gut. Furthermore, probiotics improve intestinal barrier function by promoting mucin protein production, controlling the expression of tight junction proteins such as occluding and claudin 1, and modulating the gut immune response. Probiotics also stimulate the generation of anti-inflammatory cytokines, interact with intestinal epithelial cells, and attract macrophages and mononuclear cells [39]. Probiotics can use the gut-brain axis to produce neurotransmitters in the stomach. Certain probiotic stains can regulate serotonin, gamma-amino butyric acid (GABA), and dopamine levels, impacting mood, behaviour, gastrointestinal motility, and stress-related pathways [40].

SELECTION OF PROBIOTIC STRAINS FOR BRAIN HEALTH BENEFITS:

The gut microbiota is made up of a variety of bacterial species that coexist harmoniously with their human hosts in the gastrointestinal tract [41]. Different probiotics, such as Lactobacillus plantarum, Bifidobacterium, Pseudocatenulatum, E. coli, and other combinations, can work as antioxidants, anti-inflammatory, or anti-pro-inflammatory cytokines, releasing cytokines that lower the likelihood of ND in patients [42].Probiotic bacteria that can produce acetylcholine, such as Lactobacillus plantarum, may be able to prevent memory loss brought on by D-galactose ingestion. According to Mehrabadi and Sadr (2020), probiotic strains L. reuteri, L. rhamnosus, and B. infantis (1010 CFU/day) can be used to reduce inflammation and oxidative stress in rat models of AD for a period of 10 weeks. In a 2017 study, Nimgampalle and Kuna assessed the anti-Alzheimer characteristics of L. plantarum MTCC1325 in AD rat models and documented its benefits against D-galactose-induced AD [43]. Bifidobacterium breve (B. breve) strain A1 administration improved hippocampal learning and memory in Parkinson's disease-modelling rats. Postsynaptic density protein-95 (PSD95) is a synaptic protein involved in synaptic development and stability. B. breve A1 supplementation restored the transcriptional-level expression of these two proteins (Ishii et al., 2021). It's possible that adding a probiotic cocktail that includes Bifidum, B. longum, L. rhamnosus, L. rhamnosus GG, L. plantarum LP28, and Lactococcus lactis subsp. lactis to mouse models of Parkinson's disease has enhanced motor neuron function [44].

EFFECTS OF PROBIOTICS FOR COGNITIVE FUNCTION:

Probiotics are good bacteria that alter the makeup and function of the gut microbiota (improving nutrition absorption and digestion), and they may also control the immune system and host epithelial responses. They are crucial in preserving immunological homeostasis [45]. Elderly people frequently experience cognitive impairment, which is linked to aging and dementias like Alzheimer's disease (AD).Dementia is a chronic or progressive syndrome; disease progression is too advanced when dementia becomes clinically obvious and thus, treatment is difficult. Therefore, it is becoming more important to prevent the onset of the disease before the diagnosis through improvement in lifestyle or diet. Recent research has demonstrated that certain probiotics affect behaviour and the central nervous system (CNS) through the microbiota-gut-brain axis. Models has demonstrated that certain probiotics possess the ability to modulate the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, administering probiotic supplements to mice induced by stress has been proven to reduce anxiety-like behaviour. Additionally, Akbari et al. found that probiotic-supplemented milk may have an impact on patients' metabolic and cognitive status in AD patients. Thus, a developing field of research into successful therapeutic treatments for AD and general dementia involves modulating the gut flora using probiotics or other dietary interventions [46]. Probiotics have anti-inflammatory properties, and neuronal function in the brain and cognitive processes can be affected by inflammatory reactions. It is important to remember that some vitamins and minerals, which are essential for the brain and cognitive processes, are also produced by gut microbes. Probiotics may be able to mitigate and decelerate the aging-related deterioration in cognitive function [47].

EFFECTS OF PROBIOTICS IN NEURODEGENERATION:

A normal physiological decline that comes with aging is the driving force behind both oxidative damage and inflammation, two primary systemic diseases that exacerbate neurodegeneration. The mitochondria are the primary site of the generation of reactive oxidative species (ROS), where 0.4–4% of electrons passing through the electron transport chain (ETC) escape and combine with an oxygen molecule to produce a

superoxide radical. Because neurons have high energy requirements and are nearly exclusively post-mitotic cells, their membranes rich in polyunsaturated fatty acids make them more vulnerable to ROS-induced peroxidative damage, which makes the brain particularly vulnerable to oxidative damage [48]. Inflamm-aging' is a term used to describe a chronic, low-grade systemic pro inflammatory state that is characterized by higher cytokines and inflammatory mediators without a precipitating cause. It is a vicious loop created by the pathophysiology of oxidative damage and inflammation [49]. Probiotics may help Parkinson's disease (PD) if they encourage the gut bacteria to produce antioxidant compounds like vitamins. Lactobacilli and Bifidobacterium are probiotic strains that have the ability to produce natural antioxidants, vitamins, and bioactive compounds. This means that they may be able to reduce the number of free radicals in the body and provide benefits for conditions like Parkinson's disease (PD) that are linked to oxidative stress. Due to increasing insults such as oxidative stress, chronic inflammation, reduced neurotransmitter levels, and apoptosis, it is well known that age is a main risk factor for neurodegenerative disorders. Patients suffering from Parkinson's and Alzheimer's diseases also frequently have gastrointestinal comorbidities Probiotics' ability to reduce inflammation, produce short-chain fatty acids, and stimulate the release of different neurotransmitters are some of their benefits in treating neurological illnesses [50].

FUTURE DIRECTIONS:

Probiotics' potential as therapeutic agents for mental health issues, their ability to improve cognitive function, and our growing understanding of their involvement in the gut-brain axis are the main directions for their future developments in brain health.

1. Effects of Personalized Psychobiotics: Research in the future is probably going to concentrate on determining which probiotic strains are most beneficial for various illnesses related to brain health. Since different strains of probiotics work better for different problems, such as anxiety, depression, or cognitive loss, it's important to know which ones to use. Psychobiotics treatments are specific to each patient's microbiome profile.
2. Targeting Neuroinflammation and Neurodegeneration:

   A) Neuroprotective Effects: Since neuro inflammation is linked to neurodegenerative illnesses like Parkinson's and Alzheimer's, probiotics may be investigated for their ability to lower it. Subsequent research endeavours will examine their capacity to augment brain-derived neurotrophic factor (BDNF) and additional neuroprotective drugs.
   B) Treatments for Neurodegenerative Illnesses: Probiotics may be able to postpone the onset or reduce the rate at which neurodegenerative illnesses advance. The ways in which probiotics affect neurodegeneration and how to incorporate them into treatment plans will be the main areas of research.

3. Enhancing Cognitive Function:

   A) Cognitive Enhancement: The possibility that probiotics can improve memory, learning, and executive function is a topic of increasing attention. Clinical trials examining these benefits in healthy individuals as well as those with mild cognitive impairment or dementia may be the direction of future directions.
   B) Gut-Brain Modulation for Cognitive Health: By comprehending how probiotics affect the connection between the gut and the brain, new treatments to improve cognitive function and stave off cognitive decline can be developed.

4. Mental Health Applications:

   Adjunct therapy for mood disorders: Conditions linked to stress, anxiety, and depression may benefit from the use of probiotics as an additional treatment. Large-scale clinical trials will probably be conducted in the future to confirm their effectiveness and identify the best strains and dosages.

5. Development of Novel Psychobiotics

A) Finding New Probiotic Strains: Investigations into new bacterial strains that exhibit psychotropic properties will persist, with the goal of creating new psychobiotics that concentrate on the health of the brain.
B) Combination Therapies: By combining probiotics with other therapeutic drugs, nutritional supplements, or prebiotics, their effects on brain health may be amplified, providing a more all-encompassing course of treatment.

CONCLUSION:

In summary, probiotics have great therapeutic promise for improving brain health by modifying the gut microbiome-brain axis. Research indicates that some probiotic strains may have a beneficial effect on neurochemical pathways, lessen neuroinflammation, and enhance emotional and cognitive functioning. Current research emphasizes the need for more studies to confirm these advantages and establish efficacious probiotic treatments, even though clinical applications are still in the early stages of development. A better comprehension of the link between the microbiota and the brain may result in the development of novel microbiota-based therapeutics that offer cutting-edge approaches to the management and prevention of neurological and psychiatric illnesses.

REFERENCE:

1. Bäckhed, F., Ley, R E., Sonnenburg, J. L., Peterson, D. A., and Gordon, J. I. (2005) Host-bacterial mutualism in the human intestine. Science 307: 1915–1920.

2. Bauer, K. C., Huus, K. E., and Finlay, B. B. (2016) Microbes and the mind: emerging hallmarks of the gut microbiota brain axis. Cell Microbiol 18: 632–644.

3. Ferreiro, A. L. et al. Gut microbiome composition may be an indicator of preclinical Alzheimer's disease. Sci. Transl. Med. 15.

4. Wasilewski A, Zielińska M, Storr M, Fichna J (2015) Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. Inflamm Bowel Dis 21:1674–1682.

5. Plaza-Diaz, J., Ruiz-Ojeda, F. J., Gil-Campos, M., and Gil, A. (2019). Mechanisms of action of probiotics. Adv. Nutr. 10 (1), S49–S66.

6. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol. 2009;6(5):306–314.

7. Cryan, J. F. et al. The microbiota–gut–brain axis. Physiol. Rev. 99, 1877–2013 (2019).

8. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut micro biota on brain and behaviour. Nat Rev Neurosci. 2012;13:701–712.

9. Schroeder, F. A., Lin, C. L., Crusio, W. E. & Akbarian, S. Antidepressant- like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. Biol. Psychiatry 62, 55–64 (2007).

10. Mart'yanov SV, Botchkova EA, Plakunov VK, Gannesen AV. The impact of norepinephrine on mono-species and dual-species staph ylococcal biofilms. Microorganisms. 2021;9

11. Long-Smith C, O'Riordan KJ, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota-gut-brain axis: new therapeutic opportunities. Annu Rev Pharmacol Toxicol. 2020;60:477–502.

12. Appleton, J. (2018). The gut-brain axis: influence of microbiota on mood and mental health. Integr. Med. (Encinitas) 17 (4), 28–32.

13. Sudo, N. et al. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. J. Physiol.

14. Spiljar M, Merkler D, Trajkovski M. The immune system bridges the gut microbiota with systemic energy homeostasis: focus on TLRs, mucosal barrier, and SCFAs. Front Immunol. 2017;8:1353.

15. Brown, A.J., Goldsworthy, S.M., Barnes, A.A., Eilert, M.M., Tcheang, L., Daniels, D., et al. (2003) The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem 278: 11312–11319.

16. Dalile, B., Van Oudenhove, L., Vervliet, B. & Verbeke, K. The role of short- chain fatty acids in microbiota–gut brain communication. Nat. Rev. Gastroenterol. Hepatol. 16, 461–478 (2019).

17. Frost, G., Sleeth, M.L., Sahuri-Arisoylu, M., Lizarbe, B., Cerdan, S., Brody, L., et al. (2014) The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat Frost, G., Sleeth, M.L., Sahuri-Arisoylu, M., Lizarbe, B., Cerdan, S., Brody, L., et al. (2014).

18. Nohr MK,PedersenMH,Gille A,et al. GPR41/FFAR3 and GPR43/ FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes Endocrinology. 2013;154(10):3552–3564.

19. MacFabe, D.F., Cain, N.E., Boon, F., Ossenkopp, K.-P., and Cain, D.P. (2011) Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: relevance to autism spectrum disorder. Behav Brain Res 217:47–54.

20. Cervantes-Barragan L, Chai JN, Tianero MD, et al. Lactobacillus reuteri induces gut intraepithelial CD4(+), CD8alphaalpha(+) T cells. Science. 2017;357(6353):806–810

21. Sonner JK, Keil M, Falk-Paulsen M, et al. Dietary tryptophan links encephalogenicity of autoreactive T cells with gut microbial ecol ogy. Nat Commun. 2019;10(1):4877.

22. Yoo, B. B. & Mazmanian, S. K. The enteric network: interactions between the immune and nervous systems of the gut. Immunity 46, 910–926 (2017).

23. Phillips, R.J., and Powley, T.L. (1998) Gastric volume detection after selective vagotomies in rats. Am J Physiol 274: R1626–1638.

24. Kennedy PJ, Cryan JF, Dinan TG, et al. Kynurenine pathway metabolism and the microbiota-gut-brain axis. Neuropharmacology. 2017;112(pt B):399–412.

25. Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9:286–294.

26. Wang, F.-B. & Powley, T. L. Vagal innervation of intestines: afferent pathways mapped with new en bloc horseradish peroxidase adaptation. Cell Tissue Res. 329, 221–230 (2007).

27. Morais LH, Schreiber IV HL, Mazmanian SK. The gut microbiota–brain axis in behaviour and brain disorders. Nature Reviews Microbiology. 2021 Apr;19(4):241-55.

28. Zheng, D., Liwinski, T. & Elinav, E. Interaction between microbiota and immunity in health and disease. Cell Res. 30, 492–506 (2020).

29. Hsiao, E. Y. et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155, 1451–1463 (2013).

30. Braniste, V. et al. The gut microbiota influences blood brain barrier permeability in mice. Sci. Transl. Med. 6, 263ra158 (2014).

31. Yuan, N., Chen, Y., Xia, Y., Dai, J. & Liu, C. Inflammation- related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta- analyses. Transl. Psychiatry 9, 233 (2019).

32. Daneman, R. The blood–brain barrier in health and disease. Ann. Neurol. 72, 648–672 (2012).

33. Vitini, E.; Alvares, S.; Medina, M.; Perdigon, G. Gut mucosal immunostimulation by lactic acid bacteria. Biocell 2000, 24, 223–232

34. Salminen, S.; Isolauri, E. Intestinal colonization, microbiota, and probiotics. J. Pediatr. 2006, 149, S115–S120.

35. Reid, G.; Younes, J.A.; Van Der Mei, H.C.; Gloor, G.B.; Knight, R.; Busscher, H.J. Microbiota restoration: Natural and supplemented recovery of human microbial communities. *Nat. Rev. Microbiol.* **2010**, *9*, 27–38.

36. Hevia, A.; Delgado, S.; Sánchez, B.; Margolles, A. Molecular players involved in the interaction between beneficial bacteria and the immune system. Front. Microbiol. 2015, 80, 1363–1376.

37. Galdeano, C.M.; Perdigón, G. Role of viability of probiotic strains in their persistence in the gut and in mucosal immune stimulation. J. Appl. Microbiol. 2004, 97, 673–681.

38. Konstantinov, S.R.; Smidt, H.; De Vos, W.M.; Bruijns, S.C.M.; Singh, S.K.; Valence, F.; Molle, D.; Lortal, S.; Altermann, E.; Klaenhammer, T.R.; et al. S layer protein A of Lactobacillus acidophilus NCFM regulates immature dendritic cell and T cell functions. Proc. Natl. Acad. Sci. USA 2008, 105, 19474–19479

39. Chang, Y., Jeong, C. H., Cheng, W. N., Choi, Y., Shin, D. M., Lee, S., et al. (2021). Quality characteristics of yogurts fermented with short-chain fatty acid-producing probiotics and their effects on mucin production and probiotic adhesion onto human colon epithelial cells. *J. Dairy Sci.* 104, 7415–7425.

40. Srivastav, S., Neupane, S., Bhurtel, S., Katila, N., Maharjan, S., Choi, H., et al. (2019). Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity. *J. Nutr. Biochem* 69, 73–86.

41. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR. A human gut microbial gene catalogue established by metagenomic sequencing. nature. 2010 Mar 4;464(7285):59-65.

42. Eifler N, Vetsch M, Gregorini M, Ringler P, Chami M, Philippsen A, Fritz A, Müller SA, Glockshuber R, Engel A, Grauschopf U. Cytotoxin ClyA from Escherichia coli assembles to a 13-meric pore independent of its redox-state. The EMBO journal. 2006 Jun 7;25(11):2652-61.

43. Oroojzadeh P, Bostanabad SY, Lotfi H. Psychobiotics: the influence of gut microbiota on the gut-brain axis in neurological disorders. Journal of Molecular Neuroscience. 2022 Sep;72(9):1952-64.

44. Kumar A, Sivamaruthi BS, Dey S, Kumar Y, Malviya R, Prajapati BG, Chaiyasut C. Probiotics as modulators of gut-brain axis for cognitive development. Frontiers in Pharmacology. 2024 Feb 20;15:1348297.

45. Kobayashi Y, Kinoshita T, Matsumoto A, Yoshino K, Saito I, Xiao JZ. Bifidobacterium breve A1 supplementation improved cognitive decline in older adults with mild cognitive impairment: an open-label, single-arm study. The Journal of Prevention of Alzheimer's Disease. 2019 Jan;6:70-5.

46. Fekete M, Lehoczki A, Major D, Fazekas-Pongor V, Csípő T, Tarantini S, Csizmadia Z, Varga JT. Exploring the Influence of Gut–Brain Axis Modulation on Cognitive Health: A Comprehensive Review of Prebiotics, Probiotics, and Symbiotics. Nutrients. 2024 Mar 10;16(6):789.

47. Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. Frontiers in aging neuroscience. 2010 Mar 30;2:1224.

48. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2014 Jun 1;69(Suppl_1):S4-9.

49. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. Cellular and molecular life sciences. 2017 Oct;74:3769-87.

50. Gazerani P. Probiotics for Parkinson's disease. International journal of molecular sciences. 2019 Aug 23;20(17):4121.